

**Good Manufacturing Practices:
A Synopsis of Their Role and Rationale
in Today's Pharmaceutical Marketplace for Tubing**

Katherine L. Ulman and Dr. Patricia Rafidison

Dow Corning Healthcare

DOW CORNING

About the Authors



Katherine L. Ulman
katherine.l.ulman@dowcorning.com

Kathy Ulman is the Dow Corning Healthcare Industries global regulatory manager for quality. She earned her Bachelor of Science degree in chemistry from the South Dakota School of Mines and Technology in 1976. Following graduation, she joined Dow Corning where much of her early career was dedicated to synthesis of novel silicone monomers, polymers, and copolymers; development of silicone pressure sensitive adhesives; and defining the relationship between novel silicone materials and their impact on both drug and gas delivery rates. Kathy is a member of the American Chemical Society, American Association of Pharmaceutical Scientists, Controlled Release Society, and the International Pharmaceutical Excipient Council of the Americas. She has published and presented several papers in her field and has taught international courses on Silicones for Pharmaceutical and Biomedical Applications and Medical Adhesives through Technomic Publishing Co.



Patricia C. Rafidison
p.rafidison@dowcorning.com

Patricia Rafidison currently holds positions as both the global life sciences quality and regulatory affairs manager, and the healthcare risk manager for Dow Corning Corporation. Patricia has more than 20 years of previous experience as quality and regulatory affairs manager, for healthcare raw materials and finished products, in both the pharmaceutical and chemical industries. She is currently an executive Board member of IPEC Europe, chairs the IPEC Europe GMP committee, and is part of the WHO expert network for Quality Standards. Patricia graduated with her Ph D as a Pharmacist from the University of Paris XI, France (1979) and received her Senior MBA from the French HEC-CPA school (1995).

INTRODUCTION

Global regulation of pharmaceutical products

Today most countries worldwide have requirements for reviewing and approving pharmaceutical products or are currently working to establish them in order to ensure product quality, safety, efficacy, traceability and availability. Over the last couple of decades, significant changes have occurred in the environment of pharmaceutical regulations and these changes have required adjustments to regulatory approaches due to: increased number and complexity of products, advances in science and technologies, global harmonization, etc. As a result, regulatory agencies continue to systematically reappraise their approach to product quality regulations and are currently moving more towards:

- ↪ Risk-based decisions
- ↪ Science-based policies and standards
- ↪ Integrated quality systems
- ↪ International cooperation and harmonization
- ↪ Strong public protection

Thus, with greater regulatory focus in the pharmaceutical industry, attention increasingly turns to the rationale for various guidelines, standards and specifications and their role as blueprints for producing quality products that perform a specific function and ensure both efficacy and safety for patients. Although the ISO 9000 family of quality management standards has earned a worldwide reputation as a “quality management system” which delivers a valuable framework for quality, the standards mainly focus on the “what” rather than the “how” and the end result. In today’s environment, it truly is essential for the healthcare industry to be able to manage and trace materials used in products throughout their entire supply chain.

Good Manufacturing Practices

Adherence to appropriate Good Manufacturing Practices becomes a vital component of the successful production, handling and distribution of pharmaceutical products, but selecting the appropriate guidelines and level of GMPs can pose a challenge for developers, raw material suppliers and finished product manufacturers (e.g., fabricators).

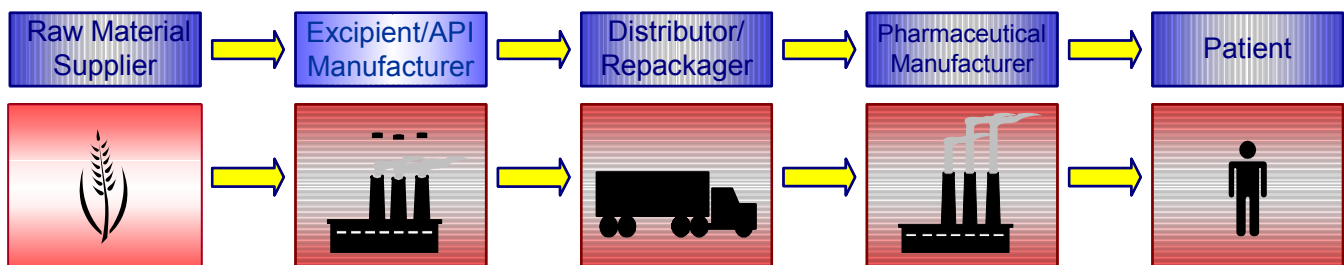
Today, government authorities in the United States, Europe, Asia, Japan and Canada can and do enforce compliance to GMPs, and similar trends are currently underway with other governmental authorities in Europe and Asia.

As a global supplier of raw materials and components to original equipment manufacturers (OEMs), fabricators and pharmaceutical producers, Dow Corning works closely with customers to ensure that designers and developers have access to a wealth of technical expertise, technical data and biosafety information. Opportunities for exchange of information with their suppliers allow OEMs to directly communicate their needs so Dow Corning can understand how its materials are being used and respond more quickly to expedite the development process. Because the OEM is responsible for final testing of their product, this approach helps Dow Corning build the proper level of quality into the product beginning with the material itself and the first steps of the development process.

GMPs and pharma tubing products

Using Dow Corning Healthcare tubing products as an example, this paper describes our “risk-based” approach for establishing appropriate quality manufacturing and handling requirements for pharma tubing products. It describes how GMPs can be used in the manufacturing environment, along with risk management and solid corporate stewardship, to guide the quality process, with the final user in mind: *the patient*.

Figure 1: Product Supply Chain



QUALITY SYSTEM REQUIREMENTS

Finished drug product regulations

Most countries around the world require review and approval of pharmaceutical products before they can be marketed and sold. These approvals are based on the applicant's ability to demonstrate that the products are manufactured and marketed in such a manner that the drugs are shown to perform a specific function and ensure both efficacy and safety for patients. This can only be achieved by paying detailed attention to identity, strength, quality and purity of the products and their components during the entire manufacturing and distribution process; therefore, various regulations and guidelines have been created to help manufacturers. Two such references are the US FDA's GMP regulation¹ and the World Health Organization's (WHO) GMP guide.²

A drug manufacturing process is a related series of operations that result in the preparation of a drug or drug product. Major operations or steps in a drug process may include mixing, granulation, encapsulation, tableting, chemical synthesis, fermentation, aseptic filling, sterilization, packing, labeling, testing, etc. Regardless of the step, it is important that at each step the drug product is protected to ensure its identity, quality, strength and purity. Thus, it is important for tubing used for filling operations to comply with principles of finished drug GMPs in order to manage for potential adulterations and mix-ups.

Bulk pharmaceutical excipient guide

In the United States, the FDA classifies articles used as components of drug products as drugs;³ thus, both active pharmaceutical ingredients (APIs) and excipients should follow principles of these drug regulations. Just as the antihistamine in a cold medicine is viewed as a drug (otherwise known as an active pharmaceutical ingredient, API) and must be manufactured under a specific set of GMPs, the same is true of the food coloring, glycerin and propylene glycol (otherwise known as excipients) and process aids (e.g., silicone tubing) used in producing the drug product.

In an attempt to help companies determine which principles of GMPs are important for excipients and process aids, both the chemical industry and pharmaceutical companies have developed a set of "self-regulating" GMP guidelines.⁴ Although not currently recognized by governmental authorities in the same way as the International Committee on Harmonization's (ICH) GMPs for APIs,⁵ the International Pharmaceutical Excipient Council (IPEC) guidelines are intended to provide general assistance and guidance targeted at helping manufacturers determine whether their methods, facilities and manufacturing practices adequately assure that the resulting products produced will possess the quality, purity, safety and suitability for use which they purport to possess.

Suppliers who do not produce these components according to principles of GMPs run a risk because regulatory authorities in the United States prohibit "the introduction or delivery for introduction into interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded."⁶ While this definition may appear clear-cut, the definition of "adulterated" is crucial: "a drug shall be deemed to be *adulterated*...if it is a drug and the *methods used in, or the facilities or controls used for its manufacture, processing, packaging, or holding do not conform with good manufacturing practices.*"⁷

General quality system considerations

While ISO 9001 is a general quality management system that is intended to be applied to any organization, large or small, whatever its product and/or service, it was developed independent of any intended use or application and was designed to allow organizations to further integrate their own, specific quality requirements into their specific quality systems.

Until the mid 1990s, ISO registration was not common in the healthcare industry, and only within the last few years have significant numbers of industry players begun to evaluate its importance (mostly for finished medical device manufacturers, using a modified quality system standard).⁸ Today, as more manufacturers and suppliers register with ISO, customers should be aware of the strengths and limitations of what ISO can provide, some of which are discussed later within this article.

SCIENCE-BASED RISK-MANAGEMENT

With the economic challenges of financing safe and cost-effective healthcare today, the reality of having to do more with less is really only feasible if what is being done in the first place is being done well. Thus, over the last couple of years many global regulatory authorities have finally realized that a prescriptive approach to applying GMPs is not only inappropriate, but also economically prohibitive. As a result, regulatory authorities globally are currently at various stages of revising their regulations to focus more on a risk-based strategy. Translated, this means that the degree of required controls, procedures, and documentation should be established based more on risk assessments (the process of identifying, estimating, and evaluating the nature and severity of risks associated with a product) than on prescriptive regulations. For example, medicines used to treat serious conditions, or which need to be used under a doctor's supervision, should be subjected to a high level of scrutiny and evaluation to determine their quality, safety and efficacy, while other products such as herbal, vitamin and mineral products may not be subjected to the same level of evaluation and may be assessed only for minimal quality and safety.

Along these lines, governmental authorities are beginning to focus more inspections on sites at the greatest risk of impacting product quality and consistency (such as new facilities, those making new or high-risk drugs, or those with a recent history of inspection issues) and less on sites that have a proven track record. It is hoped that this will lead to fewer, more efficient, science-based inspections resulting in more consistency with focused resource on critical issues.⁹ Risk management should be a continuous process of (1) learning about and interpreting benefits and risks, (2) designing and implementing interventions to minimize risk, (3) evaluating interventions in light of new knowledge that is acquired over time, and (4) revising interventions when appropriate.¹⁰

With these trends in mind, it is important to understand some of the risks associated with a specific product, application or intended use.

Learning about and interpreting benefits and risks

Just as there are different types of risks for the customer, business, patients, and for noncompliance to regulations, there are several factors to consider when

defining risk. In the case of pharmaceutical processing, it is important to demonstrate that the tubing is not reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

Some additional key criteria to consider when assessing tubing and tubing suppliers include:

- Quality system and practices
- Level of supply chain integration
- Traceability throughout supply chain
- Developmental knowledge (toxicology, stability, processing, etc.) of materials
- Acceptable risk levels (for process, product, business, application, etc.)
- Number and type of products at a given site
- Process steps (number and complexity)
- Customer and supplier expectations or agreements
- Potential to contain extractables and/or attract contaminants
- Product function (impact on availability of active, preservative, etc.)

It is important to remember that risk is not an absolute concept, but rather, an assessment of the potential of a product to do harm to those it is intended to help, or to others (such as children) who may come in contact with it—regardless of whether the harm results from following or disregarding the directions for use.

Designing and implementing interventions to minimize risks

If a laboratory setting requires movement of fluid from one place to another as part of a process, but the fluid doesn't require analysis and its purity is not significant to the final product, tubing made according to GMPs probably would not be considered or needed. In contrast, pharmaceutical manufacturers using tubing to transport fluid from one reactor to another must depend on critical quality compliance—and for that reason, it is more important to understand what effect the transport mechanism has on the identity, strength, quality and purity of the fluid withdrawn from the tanks. Elements such as impurity profiles, stability, decomposition products, etc. should be well understood. If silicone tubing is chosen over PVC in an attempt to avoid extractable materials, it is still important to understand, control, and minimize impurities; manage for contamination during extrusion and fabrication; and ensure that the inside of the tubing is clean.

Purchasing tubing from a source that operates according to the appropriate level of GMPs should provide the pharmaceutical manufacturer confidence in its suitability. Purchasing tubing from a source that may not operate according to the appropriate level of GMPs could pose added concerns, especially if a quality upset occurs and the supplier cannot identify specific batches for the material, or if there is no record of unusual events, which makes it difficult to determine the reason for the upset. If the root cause is never found, there is no way of knowing for certain that it will not occur again.

Evaluating interventions in light of new knowledge that is acquired over time

Just as managing for identity, strength, quality and purity of the products and their components during the entire manufacturing and distribution process are important, so too is making sure that any change in process, product, raw materials, packaging, etc. is properly managed to ensure that the change does not impact the drug product's performance criteria.

Even changes that may appear to be minor to a manufacturer (e.g., changing a raw material supplier, in-process control, manufacturing location) could become significant if not properly managed. For example, if an operation were moved from one location to another location within the same site, a change in operators, training, environmental controls, cleaning agents or procedures could have an impact on the quality (due to process knowledge or expertise) and/or purity (due to potential contamination) of the product produced, even though the end-product might still meet all of its defined performance criteria.

For this reason, it is important for raw material suppliers to understand, develop and manage a change control and customer notification program to meet *exactly* what their customers need.

MERGING SCIENCE-BASED RISK MANAGEMENT WITH AN INTEGRATED QUALITY SYSTEM

On the surface, Good Manufacturing Practices and other standards may appear redundant and overwhelming. If a particular site were registered to an ISO quality management standard, it might appear that this would be sufficient evidence of attention to quality. Although ISO standards remain the foundation for good quality systems and provide documented methods for demonstrating value to customers, ISO quality standards are currently voluntary and there is no ramification or penalty for noncompliance to the standard, other than potential breach of contract with a customer or loss of business. In contrast, various governmental agencies e.g., US FDA and Canada's HPFB) can and do enforce compliance to GMPs, thus differentiating them from ISO standards, and elevating their relative importance. Similar trends are currently underway with other governments in Europe and Asia.

(There are, however, a variety of different GMP regulations and guidelines based on different product applications.¹¹ Figure 2 shows some examples of areas where additional GMP criteria should be considered for materials being targeted for pharmaceutical applications.

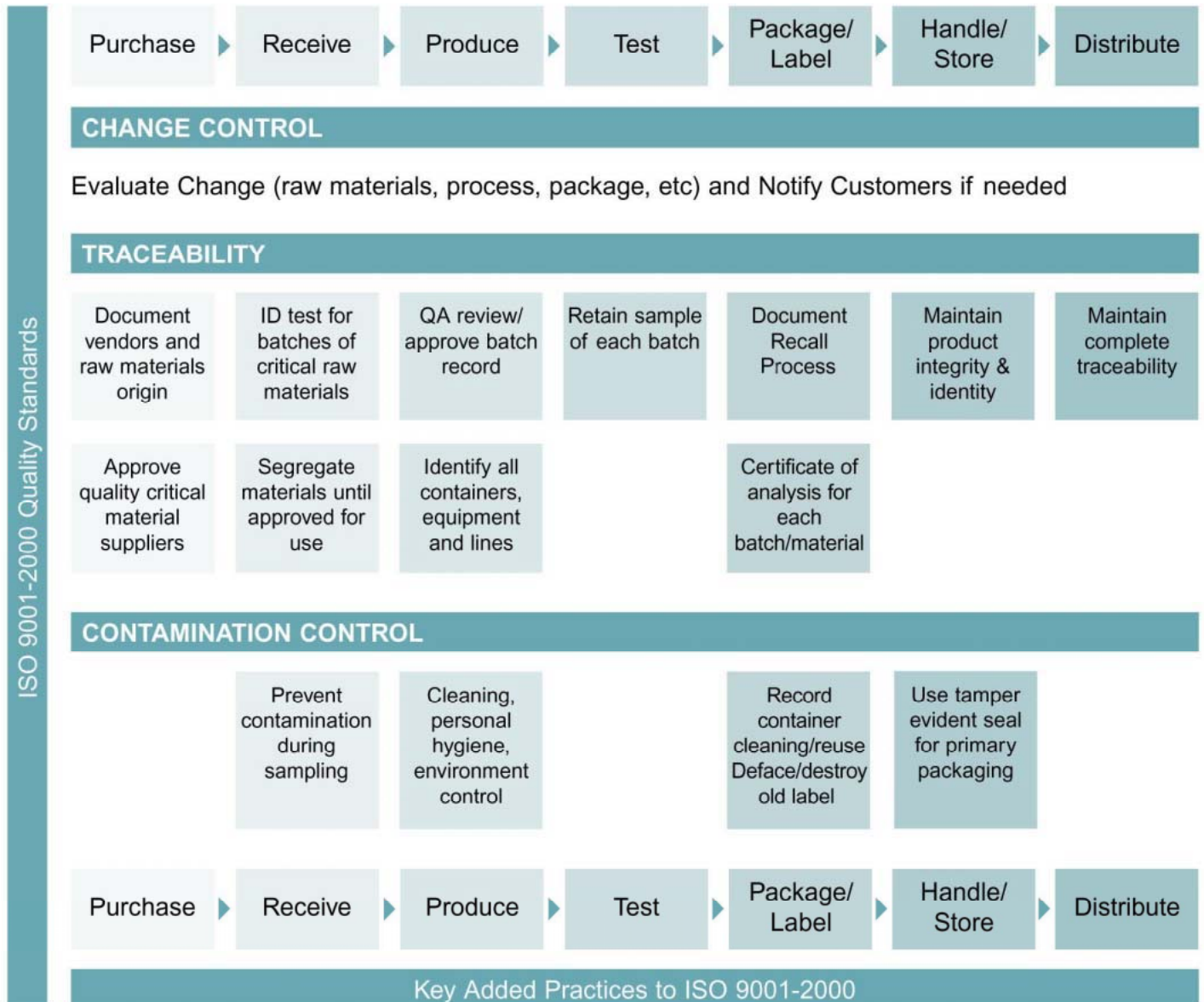
The Dow Corning Approach

After assessing potential end-use risks (based on criteria previously mentioned) and using principles of the integrated quality system approach defined above, Dow Corning has aligned its manufacturing practices and procedures to provide customers with the proper level of product quality to meet their end-user application needs. Whereas our active pharmaceutical products are produced to *comply* with finished drug product GMPs,¹² our components (such as tubing) and excipients used to support finished drugs are manufactured with the proper level of controls to manage for contamination, traceability, and change(s), including customer notification of change, when applicable.

Using tubing intended for pharmaceutical processing as an example, in addition to requirements defined by the ISO 9001:2000 Standard, we properly document and control for the origin of raw materials, retain samples of each batch produced, implement an appropriate stability program, develop and understand impurity profiles, monitor and control for sources of potential contamination (e.g., environmental, personnel, equipment aids such as lubricants and oils,

cleaning agents), assess and manage change, as well as customer notification of change and ensure traceability of product and process throughout the supply chain (receipt through delivery). We achieve this by integrating relevant GMP concepts into our procedures and policies and providing all employees at Dow Corning's Healthcare Industries Materials Site with the proper level of product, process and quality system training.

Figure 2: Integrating GMPs into an ISO 9001:2000 Quality System Program



THE ULTIMATE “QUALITY” GOAL: PATIENT SAFETY

The value of GMPs in combination with ISO standards and other quality guidelines becomes even more apparent when one considers the evolving status of regulations in the marketplace today. Globally, the creation of laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products is escalating. At the same time, industries are becoming more international and seeking new global markets. Through all of these changes it is critical for suppliers and manufacturers to remember that quality is a vital issue that ultimately affects patients. Patients and their families need assurance that drugs are safe in terms of the identity, purity and dosage level and that they will be available when they need them. Drug manufacturers can gain an added measure of confidence and control of their products if they can be assured that suppliers involved throughout their manufacturing supply chain consider their materials fit for use in healthcare applications.

In its role as a material supplier, Dow Corning capitalizes on the benefits of GMPs to produce quality products to meet exactly the needs of its fabricators and customers, which in turn translates to effective products reaching patients. Although we recognize that ISO registration plays an important role in manufacturing quality, we believe that it is not the total quality solution for healthcare applications. With an entire quality system based on GMP principles and practices, we believe that we comply not only with the letter of the law, but also with the spirit of the regulations—and in the final analysis, this is quality designed for the healthcare industry and *for patients*.

REFERENCES

1. 21 CFR 210/211 Current Good Manufacturing Practice for the Manufacture, Processing, Packing, or Holding of Drug
2. [Good Manufacturing Practices for pharmaceutical products: main principles](#) -TR 908, Annex 4
3. Section 201(g)(1)(D) of the United States Federal Food, Drug and Cosmetic Act
4. International Pharmaceutical Excipients Council (IPEC) Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, 2001
5. International Conference on Harmonization (ICH) [Q7A: GMP for Active Pharmaceutical Ingredients Recommended for Adoption at Step 4 of the ICH Process on 10 November 2000 by the ICH Steering Committee](#)
6. Section 301(a) of the United States Federal Food, Drug and Cosmetic Act
7. Section 501(a)(2)(B) of the United States Federal Food, Drug and Cosmetic Act
8. International Organization for Standardization, ISO 13485:1996 Quality systems – Medical devices – Particular requirements for the application of ISO 9001
9. FDA presentation on Integrating CMC Review and Inspection: Summary of Stakeholder Comments (5/19/2003) <http://www.fda.gov/cder/GMP/breakout-CMC/index.htm>
10. March 2003, Concept Paper: Risk Management Programs <http://www.fda.gov/cder/meeting/riskManageII.htm>
11. The GMP Letter, 11/2002, Page 1
12. Dow Corning's Healthcare Industries Materials Site at Hemlock, Michigan has been registered as ISO 9002/9001 since 1989 and is registered with and audited by the FDA as a drug establishment, registration number 1816403.

While Dow Corning believes the information to be accurate at the time it is provided, **DOW CORNING DOES NOT MAKE ANY WARRANTY OR REPRESENTATION, EXPRESS OR IMPLIED, WITH RESPECT TO THE ACCURACY, COMPLETENESS OR UTILITY OF THE INFORMATION CONTAINED IN THIS DOCUMENT OR OTHERWISE FURNISHED.**

In providing this information to you at this time, Dow Corning does not undertake to monitor further developments in the field or to provide further information to you.

Dow Corning provides this document solely for your internal use. Third parties may not use it or rely upon it. No third party obtains any right of any kind from this document or your use of it.

This document is not intended as, nor should it be relied upon as, legal advice, either generally or with respect to your specific situation. For advice about specific facts and legal issues, you should consult your own legal counsel.

TO THE FULL EXTENT PERMITTED BY LAW, DOW CORNING DISCLAIMS ANY AND ALL LIABILITY WITH RESPECT TO YOUR USE OF, OR RELIANCE UPON, ANY INFORMATION, PROCEDURE, CONCLUSIONS OR OPINION CONTAINED IN THIS DOCUMENT OR OTHERWISE FURNISHED.

We help you invent the future. is a trademark of Dow Corning Corporation.

©2003 Dow Corning Corporation. All rights reserved. No part of this work may be reproduced or transmitted in any form by any means, electronic or mechanical, including but not limited to photocopying or recording, or by any information storage or retrieval system without permission in writing from Dow Corning Corporation.

Printed in USA

Form No. 52-1045-01



*We help you
invent the future.*™

www.dowcorning.com